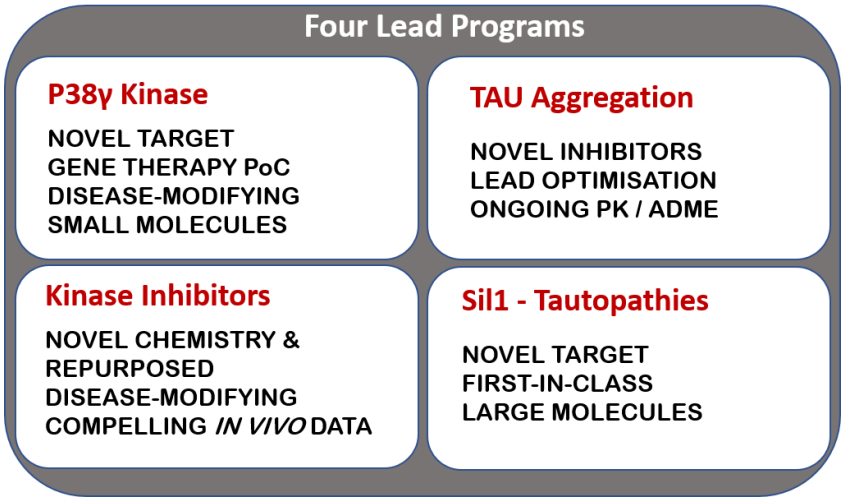
MACQUARIE University

Dementia Research Centre: Alzheimer's Disease Portfolio

EXECUTIVE SUMMARY

- **Dementia Research Centre** at Macquarie University (Sydney, Australia) has built a versatile portfolio of therapeutic approaches focusing on Alzheimer's Disease and related Dementias, with additional footprint in ALS and epilepsy.
- The Centre is well placed for strong industry partnerships and de-risked investments, having significant expertise, capabilities and multiple shots-on-goal to develop novel treatments for neurodegenerative diseases of high unmet need.
- **Four lead programs** and ~ 10 discovery-stage targets are the basis of a strong **neurodegenerative diseases pipeline,** focusing on **differentiated disease biology** areas and **in-house discovered** targets, with deep understanding of MoA and disease genetics.
- Further supported by a discovery platform, drug development program, assay systems and a **large rodent model collection** (globally used, developed in-house).
- Strong **target validation** data incl. industry-standard assays and links to disease genetics and patient samples.
- Compelling **disease-modifying Proof-of-Concept** data in gold-standard animal models and **novel chemistry**.



ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most prevalent neurological and neurodegenerative condition in humans, characterised by progressive loss of cognition resulting eventually in the inability to cope with daily living. It is the 6th leading cause of death affecting 1 in 3 seniors and the leading cause of demetia. Nearly 44 million people worldwide have AD or related dementias, with numbers expected to triple by 2050. There is no cure for Alzheimer's disease and therapeutic options are limited to modest symptomatic relief, without preventing disease progression. There are no disease-modifying drugs available. Many clinical trials have failed in the past, due to incomplete understanding of the molecular targets and pathways, failure to show target interaction of drugs and poor pre-clinical study design. The current market for AD drugs is ~$US3.64 billion, with the predicted market value of a new drug for AD being in excess of US$1 billion.

THE TEAM

The Dementia Research Centre at Macquarie University consists of 7 research teams covering different aspects of dementia research. **Core expertise** (operating own facilities) includes: Primary cell culture, Adeno-associated virus (AAV) core, Transgenic/CRISPR core and Behavioural core. Centre's Director, Prof Lars Ittner, is a world leader in dementia research with >120 publications including in leading journals (Cell, Science, Nature). His key collaborators include an international leader in CNS drug discovery and medicinal chemistry, Prof Kassiou. Ittner and Kassiou have a successful long-standing track record of joint projects, articles and funding.

"Developing novel treatments requires a detailed understanding of the molecular disease mechanisms driving neurodegeneration and dementia"

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LEAD PROGRAM #1

TARGETING P38 GAMMA KINASE TO TREAT TAU-MEDIATED TOXICITY

Alzheimer's disease brains are characterised by the deposition of two proteins; amyloid-β in extracellular plaques and tau in intracellular tangles. Current understanding is that amyloid-β is toxic to cells much before its deposition, causing neuronal dysfunction and death. Tau is thought to mediate the toxic effects of amyloid-β on neurons. Prof Ittner's team published a paradigm shifting finding (*Cell*, 2010) that the dependence of amyloid-β toxicity on tau has a mechanistic link related to dendritic function of tau and excitotoxicity. They further identified a novel molecular pathway that limits the neurotoxicity of amyloid-β in Alzheimer's disease. The unique p38 MAP kinase, p38γ, mediates the uncoupling of tau from synaptic receptor complexes and thereby prevents amyloid-β from excreting its toxic effects on neurons (*in vivo* studies in AD mouse models). The team has deciphered the molecular Mechanism of Action down to the exact amino acids involved, including revealing the first physiological and pathological function of p38γ *in vivo*. Due to its unique neuronal localisation and function in comparison to other P38 MAP kinases, it represents a promising target for therapeutic intervention.

This approach differs significantly from amyloid-β targeting methods: it prevents the toxic effect of amyloid-β on neurons, by enhancing a naturally occurring process that limits its toxicity.

1) Gene therapy - Proof of Concept

A gene therapy approach is used to enhance p38γ activity specifically in neurons, without compromising possible functions in other cells. This is achieved by delivering adeno-associated viruses (AAV) containing a neuron-specific promoter to drive expression of a genetically modified version of p38γ that has increased activity. An AAV-based gene therapy has recently been approved by FDA and has demonstrated an acceptable safety profile in numerous human clinical trials.

Therapeutically enhancing p38γ activity **prevented the memory deficits** in an established mouse model of AD with expression of the pathogenic amyloid-β and extracellular plaque formation (Morris water maze test). With more relevance to AD therapy, enhancing p38γ activity **reduced established memory deficits** in aged Alzheimer's disease mice, that were treated with AAV at 1 year of age (Nb. onset of memory deficits in this AD model is at 2-3 months of age).

Safety of activating neuronal p38γ: prolonged activation of p38γ over several months (genetically and therapeutically) had no adverse effects on brain development and function, as determined at the histological, functional (behaviour and memory testing) and neuronal network levels (EEG recordings), nor were overt side effects noticed. These findings indicate an opportunity for a broad therapeutic window using this approach.

Target engagement during therapeutic intervention in AD mouse models has been confirmed biochemically. A range of p38γ knockout and transgenic mouse models has been generated to provide a **complete pre-clinical toolset for translation**. Expression plasmids and animal models are ready to initiate AAV vector development and treatment.

2) Small molecules

Compelling therapeutic effects of a gene therapy approach in several established mouse AD models led the group to pursue the development of a small molecule activator of p38γ. First lead series of P38γ activators have been tested.

Intellectual Property: National Phase filing in key jurisdictions (AU, EP, JP, US) that protects the target, method of treatment and the relevant mouse model. Further protection will be sought for novel small molecule P38γ activators (currently undisclosed with significant know-how).

Key publications: Ittner *et al* 2010 ***Cell*** 142; Ittner *et al* 2016 ***Science*** 354; Ittner 2018 ***Neuron*** 99.

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LEAD PROGRAM #2

SIL 1 – NOVEL THERAPEUTIC TARGET FOR TAUTOPATHIES

Aberrant phosphorylation, aggregation and deposition of the microtubule-associated protein tau is a feature of a wide range of neurodegenerative diseases, commonly referred to as tauopathies. This includes rare forms of frontotemporal dementia (FTD) with isolated tau pathology, such as FTDP-17 and progressive supranuclear palsy (PSP). Both FTDP-17 and PSP are associated with rapidly progressing functional deficits, death within 2-10 years of diagnosis and absence of therapy. Advances in the field and understanding of underlying genetics increasingly enable identification of tau pathology cases.

A strong body of evidence generated by Prof Ittner's team shows that the nucleotide-exchange factor Sil1 is involved in the pathogenesis of tau-pathology in FTD. SIL1 levels are increased in FTD with tau pathology, and Alzheimer's disease. Specifically, the reduction of SIL1 (i.e. heterozygote knockout) sufficies to **mitigate tau pathology** (phosphorylation, aggregation and deposition), **prevents neuronal death** and **improves behavioural deficits in 3 independent transgenic mouse models**, expressing different isoforms of human tau together with different pathogenic FTD mutations. Conversely, *in vitro* data shows that increasing SIL1 levels augments tau-induced cell death.

Heterozygote mutant mice show no significant pathological or behavioural changes. No alterations to ER stress in tau transgenic mice were found upon reduction of SIL1. To date, there is no report that implicates SIL1 in tauopathies, including FTD and AD. Taken together, reduction of SIL1 function (i.e. heterozygote knockout) is not associated with deficits in mice, but improves tau pathology. Therefore, inhibiting SIL1 function partially may prove therapeutically efficient without compromising neuronal function.

Stage of Development

Novel, **first-in-class** Sil1 inhibitors are currently under development. There are no known Sil1-targeting molecules. FTDP-17 and PSP are seen as the prime patient group for advancing SIL1-targeting compounds into initial clinical trials. However, tau pathology is also a key feature of AD, where it contributes significantly to disease progression and spreading. Therefore, a treatment targeting tau pathology via SIL1, once established for FTD, could be extended to AD.

Intellectual Property:

National Phase filing in key jurisdictions (AU, EU, US) protecting the target and method of treatment. Further patents will be filed to cover novel Sil1 inhibitors (undisclosed with significant know-how).

LEAD PROGRAM # 3

NOVEL POLYPHENOLIC TAU AGGREGATION INHIBITORS

Preventing tau aggregation and/or dissolving pre-existing aggregates of tau has been proposed as viable strategy to treat AD, with the first compound (TauRx Therapeutics) in phase 3 clinical trials. Prof Ittner recently reported that the naturally occurring polyphenolic compound altenusin is a powerful inhibitor of tau aggregation and prevents tau pathology in cellular disease models (*ACS Chem Neurosci, 2017*). The inhibitor showed a strong propensity to prevent and dissolve tau aggregates, with oxidation of tau as a possible mechanism for preventing aggregation. Phosphorylation of tau was reduced in the presence of the inhibitor, and it prevented induction of tau pathology in primary neurons in a dose-dependent manner. However, CNS bioavailability of the inhibitor needs to be improved for clinical applications.

Stage of Development: **Lead optimisation**

- Critical components of the lead chemical structure that confer its anti-aggregation activity have been identified
- Key molecular sites for lead optimisation were identified → a unique library of lead analogues has been created
- Lead compounds prevent tau oligomers and fibrils *in vitro*, and seeding of tau pathology in a cellular spreading assay.
- Ongoing ADME/PK assessment in mice. Drug-like leads will be progressed into *in vivo* disease models.

Intellectual Property:

Undisclosed. Composition of Matter patent filing in preparation

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LEAD PROGRAM # 4

NOVEL NEUROPROTECTIVE KINASE INHIBITORS FOR DEMENTIA

- Novel and repurposed compounds targeting a specific, undisclosed kinase
- **Compelling *in vitro* and *in vivo* data** sets, showing positive effects in Alzheimer's Disease models. In particular, the compounds **reverted established functional deficits** (memory impairment and neuronal network aberrations) in relevant preclinical mouse models of AD.
- The compound can be delivered systemically and has no overt side effects.

Intellectual Property: Patents being filed. More information available under CDA.

ANIMAL MODELS

- The Centre currently handles **more than 80 diverse mouse models** of dementia. Examples below include in-house developed, globally accepted models.
- Existing and past collaborations with international pharma for pre-clinical drug testing.

1. Mutant amyloid-β precursor protein (**APP**) mouse model of AD E.g. APP humanized lines
2. **Tau models**:
   - **Δtau74** (Ittner *et al* 2010 *Cell* 142) – truncated tau (aas 256–441 removed from the longest human tau isoform, htau40) expressed under control of the murine Thy1.2 promoter);
   - **TAU58/2** (van Eersel…Ittner *et al* 2015 *Neuropathol Appl Neurobiol* 41(7)) - P301S mutant tau transgenic mouse line)
3. **p38γCA** transgenic mice (Ittner *et al*, 2016 *Science* 354) – neuronal expression of constitutive active p38γ in CNS
4. **p38γ** knockout and transgenic mouse models (Ittner *et al* 2016 *Science* 354) – global knockout of p38γ
5. **iTDP-43^{A315T}** (Ke *et al* 2015 *Acta Neuropathologica*) – Model of Frontotemporal Dementia (FTD) and Motor Neuron Disease (MND, aka ALS). This model is currently used by several international and Australian collaborators and for drug testing with international pharma

OTHER PROGRAMS AT DISCOVERY STAGE

- Disease mechanism in AD and related neurodegenerative conditions
- Mouse models for AD, tauopathies and ALS
- Neuronal 3D cell culture models of AD

PARTNERING OPPORTUNITY

- We are seeking an industry partner for further development and commercialisation of the outlined research programs, through flexible, mutually beneficial partnership arrangements, such as research collaborations, technology licence (incl. Option to Licence) and spin-out models.
- Research investments in Australia can be leveraged through generous R&D Tax Offsets for Australian subsidiaries (43.5% refund) and a variety of commercial grant schemes (incl. matched funding).

WOULD YOU LIKE TO KNOW MORE?

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